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BIOMARKERS OF ENDOTHELIAL ACTIVATION AND ATP-BINDING CASSETTE TRANSPORTER A1 (*ABCA1*) GENE VARIANTS IN SUBJECTS WITH LOW HDL-C CONCENTRATION

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AUTHOR'S DECLARATION

I declare that the work in this thesis was carried out in accordance with the regulations of Universiti Teknologi MARA. It is original and is the results of my own work, unless otherwise indicated or acknowledged as referenced work. This thesis has not been submitted to any other academic institution or non-academic institution for any degree or qualification.

I, hereby, acknowledge that I have been supplied with the Academic Rules and Regulations for Post Graduate, Universiti Teknologi MARA, regulating the conduct of my study and research.

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ABSTRACT

Soluble vascular cell adhesion molecule-1 (sVCAM-1), intercellular cell adhesion molecule 1 (sICAM-1), and E-selectin are biomarkers reflecting endothelial activation (EA), a key event in atherosclerosis. High-density lipoprotein cholesterol (HDL-c) is protective against atherosclerosis by reverse cholesterol transport (RCT) but its association with EA is not well established. ATP-binding Cassette Transporter A1 (*ABCA1*) is the main transport protein in RCT and its gene variants have been linked to low HDL-c concentration. Thus, this study aimed to (a) compare the concentration of biomarkers of EA between low HDL-c subjects and normal controls (NC), (b) examine the correlation and association between HDL-c and biomarkers of EA, (c) investigate whether HDL-c concentration is an independent predictor for these biomarkers, and (d) determine the genetic variants of *ABCA1*. A total of 207 subjects with low HDL-c and 215 age-, gender-, ethnic-, smoking-, diabetic- and blood pressure-matched NC were recruited. Fasting blood samples were collected for biomarkers of EA and DNA extraction. Targeted regions of *ABCA1* gene were amplified and sequenced. The detection of the SNPs were analysed using BioEdit. Subjects with low HDL-c had greater concentrations EA biomarkers compared to controls. There were significant negative correlations and association between HDL-c concentration and EA biomarkers. HDL-c was an independent predictor for sVCAM-1. DNA sequencing of *ABCA1* revealed six genetic variants and two SNPs were found to be significantly different between the low HDL-c subjects and NC in both genotype and allele frequencies. In conclusion, low serum HDL-c concentration is strongly correlated and associated with enhanced status of EA which strongly supports its role in the pathogenesis of atherosclerosis. The findings of genetic variation in *ABCA1* suggest that this gene may play an important role in HDL deficiency amongst Malaysians.

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CHAPTER ONE

INTRODUCTION

1.1 RESEARCH BACKGROUND

Approximately $110 billion has been spent in the year 2010 alone for the cost of health care services, medications and loss of productivity in the US due to coronary artery disease (CAD), and by 2020 (Chockalingam et al., 2000) it is estimated that CAD will be the number one cause of disability and death worldwide which is nearly 25 million of death (Murray & Lopez, 1997). According to The National Health and Morbidity Survey in 2011, Malaysia was reported as having a high prevalence of chronic disease including high cholesterol. In 2010, about 40% of death in Malaysia was estimated to be caused by chronic diseases. Whilst, data from World of Health Organization published in 2014, CHD death in Malaysia reached 29,363 or 23.10% of total death in which the death rate is 150.11 per 100,000 of population.

To date, CAD remains one of the major causes of death in the developed and developing countries (Xu et al., 2013) and is commonly due to atherosclerosis, a systemic and complex disease in which lipid and fibrous material accumulate within the intimal layer of large to medium-sized arteries. It is also the most important and common underlying cause of myocardial infarction, ischaemic stroke, and peripheral vascular diseases apart from being the major cause of chronic heart failure and vascular dementia. It can start as early as foetal life (Palinski & Napoli, 2002), progressing slowly throughout childhood and adolescence and accelerating in adult life. It also involves indolent inflammation, endothelial activation, oxidative stress and prothrombogenesis (Virmani, Kolodgie, Burke, Farb, & Schwartz, 2000).

Inflammation, endothelial activation, oxidative stress and prothrombogenesis are significant contributors to the development and progression of atherosclerosis. Several biomarkers have been established to reflect the status of these processes. Biomarkers such as high sensitivity C-reactive protein (hsCRP) and Interleukin-6 (IL-6) are indicators of inflammation (Schuett, Luchtefeld, Grothusen, Grote, & Schieffer, 2009), while endothelial activation is reflected through the various adhesion molecules such as soluble vascular cell adhesion molecule-1 (sVCAM-1), soluble